Chikungunya Fever: Clinical Perspective

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ABSTRACT

Chikungunya virus is the arthropod born virus. Aedes aegypti is recongnized as primary vector. The virus is transmitted from one to another vertebrate host. The individuals having compromised immune system like new born babies are at higher risk of Chikungunya fever. Chikungunya fever is divided into three genotypes. West Africa genotype (waf) and other two are East\Central\South Africa genotype. The incubation period of Chikungunya virus is 1 to 2 weeks. On the basis of Clinical perspective, disease has two stages. During the acute stage patient feel Pyrexia, Polyarthralgia along with these muscle pain also noticed. Diarrhea is the primary GIT symptom in acute stage. Clinical stage of disease involve various body system like nervous system, respiratory system and muscloskeleton. RT-PCR, RT-LAMP and also various serodiagnostic techniques like immunofluorescence assay, haemogglutatin assay can be used for the diagnosis purpose. There is no specific treatment for the Chikungunya virus but in order to alleviate the pain and other symptoms, symptomatic treatment is given. The most important is the management of the disease. By giving appropriate analgesia, pain can be reduced. It is acute febrile disease associated with increasing prevalence and impact on public health. Chikungunya virus spreads very rapidly and cause the contamination of the large population. The only way to control the spread is the proper management by completely destroying the vector habitat. Vaacination is available against chikungunya virus, but before vaccination personal protective measurements is crucial. Besides of all these, awareness among the community play a vital role for the Control of disease.

Keywords: Aedes aegypti, Incubation period, Genotype, Polyarthralgia, serodiagnosis, RT-PCR, Vaccination.

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INTRODUCTION

Chikungunya virus (CHIKV) is spread by Aedes (Ae.) mosquitoes and belongs to the arthropod-borne virus category. Back in 1952, the CHIK virus was primarily recognised in the Makonde Plateau, previously known as Tanganyika, located in the southern province of Tanzania. CHIKV is propagated through a transmission cycle involving female mosquitoes. Aedes mosquitoes feed on the blood-containing virus from a affected vertebrate host and become infected. After an appropriate extrinsic incubation period, the virus is then transmitted from one to another vertebrate host when the mosquitoes feed again (Solignat et al. 2009). Chikungunya is a viral disease transmitted by vectors, primarily causing significant outbreaks, particularly in tropical and subtropical regions. (Weaver et al. 2012). Chikungunya fever is distinguished by an significantly elevated viraemic load, accompanied by specific abnormalities like significant lymphopenia and mild thrombocytopenia. (Thiberville et al. 2013). Chikungunya fever (CF) presents as a highly symptomatic acute illness, with severe arthralgia during the acute phase that may progress to chronic arthritis. The term "Chikungunya" originates from the Makonde language spoken in some areas of Mozambique and translates to "that which bends up," directly alluding to the arthritic symptom's characteristic of the disease (Kucharz et al. 2012). The transmigration of Chikungunya virus (CHIKV) primarily arises through mosquitoes, mainly *Aedes aegypti* and Aedes albopictus. Nevertheless, in certain regions, transmission by other mosquito species like Culex, Mansonia, and Anopheles has also been documented. Besides affecting humans, CHIKV is found to circulate within natural sylvatic environments, where it involves primates and possibly rodents as hosts and reservoirs (Pialoux et al. 2006). In Pakistan, the Chikungunya virus (CHIKV) was identified to be circulating in rodents as far back as 1983 (Darwish et al. 1983), still only a limited number of human cases have been reported. In 2011, several patients were found to have CHIKV antibodies in their bodies, during a dengue outburst in Lahore. Later, in 2016 in Karachi CHIKV emerged, and an outbreak was officially announced, once evidence of local transmission was confirmed (Aamir et al. 2017).

2. RISK FACTOR

Certain risk factors have been related to the development of a severe chikungunya fever. Females have a higher risk of progressing to a severe chronic stage of the disease compared to males. Individuals who smoke are more likely to experience a severe chronic stage of Chikungunya fever. Moreover, Patients who experience severe joint pain during the early grade of Chikungunya fever are at a greater possibility of developing a severe recurrent stage (Delgado-Enciso et al. 2018). The study indicating that newborn babies and infants (under one year of age) are highly affected to intense forms of CHIKV infection and have a higher degree of viral load are significant and have important implications for public health policies. This highlights the need for special attention and protection for this vulnerable age group, potentially through CHIKV vaccination strategies.

Given that neonates bear the greatest relative economic and health burden of CHIKV disease, the development of an effective vaccine becomes even more critical. The presentation of CHIKV infection in children can be diverse and sometimes challenging to diagnose accurately, especially in younger age groups like infants. While fever and skin rash are more apparent and easier to identify, joint-related symptoms such as arthralgia and arthritis may be less obvious, leading to potential delays in diagnosis and appropriate management, particularly in infants (Pinzón-Redondo et al. 2016).

3. VECTOR

In the Asian and North Pacific Ocean regions, the Chikungunya virus is spread through the sting of Aedes mosquitoes, which are also responsible for transmitting the dengue virus. Among these mosquitoes,

Aedes aegypti is recognized as the primary vector, while Aedes albopictus has newly arisen as an front page vector as well, which is commonly known as the Asian Tiger mosquito. *Aedes aegypti* (primary vector) primarily flourished in reservoirs of freshwater resources such as air coolers, plant pots, and water cans. These mosquitos can be found in peri-domestic areas, which include wasted household stuff like vehicular tires, coconut shells, pots, cans, and bins in rural, town and suburban areas. These flourishing sites provide favourable habitats to the mosquitoes for the completion of their life cycle (WHO 2009; Samuel et al. 2009).

4. EPIDEMIOLOG

CHIKV is considered to have its origins mainly in Central/East Africa (Powers et al. 2000). Notably, *Aedes aegypti* and *A. albopictus* mosquitoes are the main carriers accountable for the civil spread of Chikungunya fever (Powers and Logue 2007). CHIKV stands out as the most widespread alphavirus conveyed to vertebrate hosts (Zaid et al. 2021; Kril et al. 2021). While the precise details remain unclear, advanced understanding suggests that CHIKV flourished within a wild animals and vectors in both Asia and Africa, and it involves primates other than humans and Aedes mosquito's residency in forested areas. However, the transition to urban areas and subsequent human-to-human transmission is driven by two Aedes mosquitoes of the genus that possess a strong affinity for human blood over that of other animals (Weaver et al. 2020; Azar et al. 2020).

In 1952, in Tanazania outbreak of chikungunya virus has occurred and it caused a large no of both emerging and re-emerging cases of chikungunya virus across different areas of Tanazania. Notable outbreaks occurred in the following areas and periods:

A chikungunya outbreak was reported in Uganda during the 1960s and 1990s (Schuffenecker et al. 2006; Lanciotti et al. 1998). The virus caused an outbreak in Zimbabwe (Lanciotti et al. 1998) and in Senegal (Halstead et al. 1969; Diallo 1999). Countries in Central Africa, such as the Central African Republic, Democratic Republic of the Congo and Cameroon,also experienced chikungunya outbreaks (Barrett and Weaver 2012; Jupp and McIntosh 1988; Pastorino et al. 2004). Apart from these regions, chikungunya outbreaks have been reported in many other regions of the world, making it a global health concern. On the basis of their geographical distribution, Chikungunya virus has been classified into three definite forms of their genotype. The first genotype, known as the West African genotype (WAf). The other two are East/Central/ South Africa and Asia (Powers et al. 2000).

Studies conducted by Lanciotti et al. (1998) and phylogenetic analyses presented by Powers have provided genetic evidence that ONN (O'nyong-nyong virus) and CHIKV are genetically different from each other (Powers et al. 2000). The African CHIKV viruses exhibit a paraphyletic grouping suggesting past affirmation shows that the virus first appeared in Africa and then in Asia. These genetic findings shed light on the evolutionary history and geographic spread of CHIKV, showing how different strains have emerged in various other regions over time and providing valuable insights into its transmission dynamics (Powers et al. 2000; Presti et al. 2012).

5. CLINICAL SIGNS AND SYMPTOMS

Whenever a person comes in contact with chikungunya fever, there is a plethora of signs and symptoms displayed by the infected individual. The disease is marked by a sudden and abrupt onset of high fever accompanied by severe pain in joints, which can endure for weeks to even years (Suhrbier et al. 2012). The incubation period of chikungunya virus is usually between I to 2 weeks. On the base of illness duration, chikungunya fever can be divided into two forms. It can be either acute illness or chronic/late-stage illness.

5.1. ACUTE STAGE

Symptomatic individuals typically experience a sudden onset of the disease, characterized by pyrexia, pain in different joints of the body, back pain, cephalalgia, and tiredness. High-grade Fever and the distinct pathological indication manifest within one week.

Polyarthralgia, which is the pain affecting multiple joints, is recorded in 89% to 99% of cases and stands as the highly distinctive indication. The arthralgia is usually symmetrical, on both sides, and commonly affects external joints like carpus, tarsus, and appendages, along with a few larger joining of the body like shovel, arm and leg. Arthritis, on the other hand, is less common, observed in 25 to 42% of cases. Additionally, discomfort in ligaments (such as pubic inguinal pain syndrome, musculus sternocleidomastoideus, occipital inclusion, and heel pain), articular temporomandibularis and tendonitis have been reported.

In recent prospective studies, myalgia (muscle pain) was seen in 46 to 59% of cases, while contemplative studies showed greater frequency (almost 94%). Muscle pain tends to affect the elbow and legs, and pain in the back portion of the lower leg without causing inflammation of the muscles. Muscularmaculopapular or Maculopapular rashes characterized these cutaneous manifestations. Hypersensitivity, hypermelanosis, dermatitis and photosensitivity are also seen. Such complications are transient and subside soon. A general pruritus is also observed in one-fourth of the total cases. If a person already suffers from dermatoses, then there will be a sudden flare-up in that particular skin condition, as in psoriasis. In about 15-47 per cent of the reported cases presented at clinics, there are symptoms related to the gastrointestinal tract. They are specifically seen in the acute stage of disease. People affected with chikungunya fever have to suffer from stress and depression, not because the disease affects the nervous system but mainly due to the declining quality of life. Diarrhea is a primary gastrointestinal symptom in the acute stage (Thiberville et al. 2013).

5.2. CHRONIC STAGE

Now that we have talked about the different signs and symptoms accompanying with the acute stage of the disease. Let us take a close look at the symptoms of the late-stage or chronic phase of chikungunya fever. The most frequent and prolonged problem is musculoskeletal pain. Patients are also reported to have chronic rheumatic manifestations. Rheumatoid arthritis is also diagnosed in accordance with chikungunya fever. Spondylarthopathy is often interpreted as well. There are so many atypical cases with a variety of displays of signs and symptoms. It is to be noted that people who have a history of alcoholism or epilepsy display episodes of seizures. Encephalopathy and encephalitis are some major and well-known signs of nervous anomalies. Subarachnoid cerebral haemorrhages are observed as well. Symptoms such as fever, fatigue, cerebral disorders, bursitis, dysesthesia, and paraesthesia are seen, but they are not very abundant. But there is one thing that must be repeated: people report a poor quality of life after contracting the disease. Haemorrhagic symptoms are less presented, usually in only 1-7 per cent of cases. Minor bleeding from gums can be reported and that is one of the reasons not to use certain medications which will be discussed in the treatment section. Clotting abnormalities are not associated. Conjunctivitis, neuroretinitis, dry cough, pneumonia and pericarditis are also seen. Children show a very interesting pattern of symptoms of the disease. In children there is more involvement of cutaneous signs than rheumatological signs. Most commonly we can see maculopapular rashes, generalized erythema and hyperpigmentation in children when it comes to the neurological symptoms,menengial syndrome is observed. For pregnant women, this disease has no observable growing teratogenic effects fetus. Vertical transmission is a significant cause of the spread of intrapartumviremia (Thiberville et al. 2013). Chronic CHIKV disease can lead to substantial debilitation, and when large epidemics occur, the severe economic consequences underscore the significant public health threat posed by CHIKV (Mohan 2006).

6. CLINICAL SIGNS AMONG TRAVELLERS

Between January and October 2006, a group of 69 travellers with symptoms suggestive of CHIKV infection and a compatible medical history were investigated. Among them, 41 were female, and 48 experienced joint pain. A confirmed diagnosis of chikungunya fever was established in 20 patients, with 14 of them being female. The average life of those patients was 45 years, varying from 13 to 65 years.
Out of the 20 confirmed cases, 45% (9 patients) had travelled from Mauritius, 15% (3 patients) from India, and 10% (2 patients) each from Réunion, Malaysia, and the Seychelles. Additionally, 5% of the cases each were from Madagascar and Indonesia. Among these patients, 19 were German tourists on vacation, while one patient was on a student exchange in Réunion. The mean period of travel was three weeks, ranging from 2 to 26 weeks. The symptoms typically started during the travel period in 14 patients, while in 6 patients, they emerged 1 to 3 days after their return. These symptoms included fever, fatigue, headache, and myalgia (muscle pain) (Taubitz et al. 2007).

7. DIAGNOSIS

The most common and excellent procedure for determining Chikungunya fever culture media of the virus involves inoculating mosquito cell cultures, mosquitoes, mammalian cell cultures, or mice with patient samples (Simon et al. 2008; Sudeep and Parashar 2008; Chevillon C et al. 2008; Powers et al. 2007). Viral culture has the advantage of being able to detect a broad range of viruses. Alternatively, molecular tools such as RT-PCR and RT-LAMP have also been very efficient for rapid diagnosis of CHIKV. In clinical settings, serodiagnostic methods are more commonly employed for detecting Chikungunya virus infection. These methods determine the presence of several immunoglobulins like immunoglobulin M (IgM) and immunoglobulin G (IgG) against the CHIKV in acute and convalescent serum samples. Some of the serodiagnostic techniques used include enzyme immunoassay, indirect immunofluorescence microscopy, hemagglutination assay, or neutralization techniques. After two days of infection, IgM antibodies become detectable, as measured by enzyme immune assay or immunofluorescence microscopy, and can remain for 3 to 12 weeks. IgG antibodies, on the other hand, are detectable in recovering specimens and can stay for an extended period. It has been discovered that approximately 40% of symptomatic patients may still have detectable IgM antibodies even 18 months after the onset of the disease (Borgherini et al. 2008; Grivard et al. 2007). Therefore, the interpretation of these serological tests should be done cautiously, as they may need to be fully standardized.

8. TREATMENT AND MANAGEMENT OF CHIKUNGUNYA

The mild acute cases of chikungunya fever can be managed by simple measures such as resting, maintaining oral hydration, and providing appropriate analgesia. These steps help alleviate the symptoms and support the body's natural recovery process during the intense stage of the infection (Simon et al. 2015). Indeed, it is crucial to differentiate patients who have mild, uncomplicated chikungunya fever from those who present with severe forms of the disease, which necessitate medication and examination in a specific medical setting. The standard for determining the severity that requires hospitalization includes:
1. Haemodynamic failure: When there are signs of instability in the circulatory system, such as low blood pressure or poor perfusion.
2. Uncontrolled pain: If the patient's pain is not adequately managed using level 1 analgesics like aspirin or ibuprofen and level 2 analgesics like tramadol PO/IM/slow infusion.
3. Indication of haemorrhage: If there are indications of abnormal bleeding, such as injury, pinpoint haemorrhage, usually red, brown, and purple on the skin, or bleeding from a mucous membrane.

4. Comorbidities with decompensation: If the patient has pre-existing health conditions that worsen due to the chikungunya infection.
5. Atypical chikungunya fever symptoms: When the disease manifests with unusual symptoms affecting the respiratory system, heart, nervous system, liver, blood, or kidneys.
6. Patients meeting any of these criteria require immediate hospitalization and specialized medical care to manage the potentially severe complications associated with chikungunya fever (Webb et al. 2022).

9. MANAGEMENT OF PAIN

Intense pain is the most debilitating indication experienced during the acute phase of chikungunya fever. To assess and quantify pain levels, healthcare professionals routinely use verified pain estimation scales, such as the numeric rating scale (NRS). The NRS allows patients to figure their pain on a continuum from zero to ten, where zero represents no pain, and ten indicates the unfavorable pain. This range rate helps healthcare providers understand the severity of pain experienced by the victim and aids in determining appropriate analgesic interventions for pain management during the intuitive phase of chikungunya fever (Brito et al. 2016). During clinical examination of a patient with chikungunya fever, neuropathic pain is suspected, and it may be characterized by specific symptoms such as allodynia (pain triggered by an ordinarily non-painful stimulus), neuropathic pain or nerve pain, burning sensation, or numbness. In such cases, optimizing pain management requires a comprehensive evaluation using validated tools like the DNA questionnaire.
The DNA questionnaire includes both sensational description and indications associated with bedside sensory examination. It comprises four questions aimed at identifying signs of neuropathic pain, such as burning sensation, numbness, or pain from non-painful stimuli. By using this questionnaire, healthcare providers can assess the presence and severity of neuropathic pain and tailor the analgesic treatment accordingly. Identifying and addressing neuropathic pain is essential for providing effective pain relief and improving the overall management of chikungunya fever in patients experiencing these specific pain symptoms (Bouhassira et al. 2005). According to WHO guidelines, daily hydroxychloroquine or chloroquine administration for four weeks is recommended for patients experiencing musculoskeletal symptoms that are not responding well to conventional symptomatic treatment (WHO 2008). However, it is important to note that the effectiveness of hydroxychloroquine and chloroquine for treating chikungunya fever has not been definitively proven. Additionally, many other expert societies do not support the use of hydroxychloroquine and chloroquine for chikungunya fever. Their recommendations are not in favour of using these medications due to the need for substantial evidence supporting their efficacy in managing the symptoms of the disease. As with any treatment, it is the first and foremost duty of medical management staff to attentively measure the possible advantages and disadvantages before administering hydroxychloroquine or chloroquine to patients with chikungunya fever. The choice to use these medications should be according to the requirement and the medical condition of the patient, considering individual patient factors and the most up-to-date clinical evidence available (Webb et al. 2022; Lamballerie et al. 2008).

10. FUTURE STUDIES OF CHIKV

CHIKV infection leads to an acute febrile illness, with a significant number of patients experiencing persistent polyarthralgia *(*Zaid et al. 2021; Kril et al. 2021; DE Lima Cavalcanti et al. 2022; Hoarau et al. 2010). The pathogenesis of chikungunya fever is a complex process characterised by a delicate coaction of both human and viral factors. Over the past decade, significant advancements have been made in identifying the primary molecules of the host involved in CHIKV infection and immune pathophysiology

(Liu et al. 2022; Suhrbier 2019; Ekchariyawat et al. 2015). However, further research is still necessary to certify this discovery related to anatomical systems.

Despite the significant knowledge acquired from the current outburst and examination, additional research is required to deepen our understanding of CHIKV transmission. Specifically, studies exploring carrier ability and possible spread can shed light on why this Central/East African strain was exceptionally efficient in transmission. Developing susceptible and precise models that incorporate ecological, entomological, and virological factors may aid in predicting disease spread and potential future CHIKV outbreaks. Similar models have proven valuable for other phlebovirus diseases, like Rift Valley Fever (Linthicum et al. 1999).

Physicians play a crucial role in determining cases, and they should acknowledge CHIKV infections in victims with pyrexia and arthralgia, especially if there's recent travel to or exposure to individuals from CHIKV outbreak regions. Swift notification of suspected cases to local health departments is essential to facilitate early detection and implement combative carrier monitoring procedures and correspondence to prevent local transmission. It is imperative to continue researching the pathological process of consistent joint pain and explore possible medicinal, such as anti-virus, to cure CHIKV infection and mitigate its high viremia and significant morbidity. While a live, attenuated vaccine showed promise in stage 2 human tests, its growth was discontinued due to reactogenicity and low demand (McClain et al. 1998; Edelman et al. 2000). Revisiting the study of live attenuated vaccines and other immunization production, such as chimeric alphavirus vaccines, is crucial and public health officials are essential to prevent further spread—the appropriate awareness of correct detail. In the meantime, physicians should seriously educate patients travelling to the areas which are at higher risk of chikungunya infections and preventive measures involving plans to reduce the bite of mosquitoes.

Chikungunya virus has displayed its potential to spread rapidly and contaminate a considerable number of populations during recent epidemics. Taking measures to improve disease recognition, control vector populations, and promptly apply community health data to carrier management procedure experimentation can play a pivotal role in controlling the degree of future CHIKV outbursts.

11. PREVENTION

Before the availability of vaccines, the primary effective measures to prevent infection consist of personal protection against mosquito bites and controlling mosquito populations. The approach used for controlling both adult and larval mosquitoes is similar to that employed for managing dengue and has demonstrated considerable success in various countries and environments (WHO 2009). Mosquito control remains the most viable method for preventing CHIKV infection, necessitating the elimination, destruction, regular emptying, and cleaning or treatment with insecticides of breeding sites (WHO 2007).

In order to protect against mosquito bites, it is highly recommended to wear clothing that reduces skin exposure to daytime-biting vectors. Following the specific instructions written on the product label, it is helpful to use mosquito repellent against the vectors to the exposed skin and clothing. Effective repellents should contain DEET (N, N-diethyl-3-methylbenzamide), IR3535 (3-[N-acetyl-N-butyl]-amino propionic acid ethyl ester), or icaridin (1-piperidine carboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester). Further protection against indoor mosquito biting can be achieved by using mosquito coils or other insecticide vaporizers (WHO 2014).

In order to combat Chikungunya fever outbreaks effectively, it is imperative to raise awareness among public health officials and the community. For the effective vector control measures, it is essential to dispose of the nature sites, and the application of insecticides and repellants should be implemented at both in-person and population levels, as they can yield significant benefits. The effective control of vectors and surveillance play a role in minimising fever epidemics. To achieve this, it is vital to actively appoint the

community and collaborate with public health authorities to promote hygiene practices and mosquito control measures. Integrated vector management strategies aimed at reducing or interrupting disease transmission should be actively pursued.

However, due to the extensive nature of these measures, they are beyond the scope of this review. For more comprehensive information, readers are encouraged to refer to (Bhatia and Narain 2009).

12. CONCLUSION

It is typically a short-lived illness, yet during significant outbreaks, it can result in a public health and economic impact. Effective disease prevention hinges on a meticulously planned approach that also incorporates awareness regarding early warning signals. The adoption of an integrated strategy for vector management, entailing the removal of breeding sites, the use of adult and larval control measures, and the promotion of personal protective measurements, is vital in thwarting the occurrence of outbreaks. The active involvement and mobilization of communities are pivotal in the quest to prevent and manage Chikungunya.

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